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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/295,463	04/13/1999	LEX M. COWSERT	ISIS-3455	7206
35807	7590	10/13/2005	EXAMINER	
Isis Pharmaceuticals, Inc. 1896 Rutherford Road Carlsbad, CA 92008			MORAN, MARJORIE A	
			ART UNIT	PAPER NUMBER

1631

DATE MAILED: 10/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Advisory Action</b> <b>Before the Filing of an Appeal Brief</b>	<b>Application No.</b> 09/295,463	<b>Applicant(s)</b> COWSERT ET AL.	
	<b>Examiner</b> Marjorie A. Moran	<b>Art Unit</b> 1631	

**--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**

THE REPLY FILED 23 September 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on \_\_\_\_\_. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

#### AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
- (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ They raise the issue of new matter (see NOTE below);
- (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_. (See 37 CFR 1.116 and 41.33(a)).

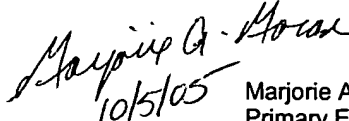
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.
6. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
- The status of the claim(s) is (or will be) as follows:
- Claim(s) allowed: \_\_\_\_\_.
- Claim(s) objected to: \_\_\_\_\_.
- Claim(s) rejected: 55,56,58-72,74-76,78-83,85-87 and 99-102.
- Claim(s) withdrawn from consideration: \_\_\_\_\_.

#### AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

#### REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:  
See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). \_\_\_\_\_
13. ☐ Other: \_\_\_\_\_.

  
 10/5/05

Marjorie A. Moran  
 Primary Examiner  
 Art Unit: 1631

Continuation of 11. does NOT place the application in condition for allowance because: In response to the argument that finality of the office action is premature, it is noted that (a) no "amendment" was, in fact, filed prior to the RCE. The previous examiner noted that IF the claim listing filed with the arguments were to be considered an amendment, it would not be entered as it was an improper amendment for the reasons listed in the advisory action of 12/9/04, (b) the RCE did not request entry of the "amendment" filed 9/13/04, but instead was accompanied by a different amendment, and (c) the amendment filed with the RCE of 2/14/05 did not change the scope of the claims, all rejections could have been made over the amended claims even if they had been presented in the previous amendment. In fact, the rejections are all the same as those made and maintained in previous office actions. Thus, the examiner maintains that the finality of the previous office action is proper, and the time period for response to the final office action continues to run from the mailing date of 5/23/05.

In response to the argument that AGRAFIOTIS does not teach use of thermodynamic criteria on combination with "other" criteria to generate in silico compounds, it is noted that applicant admits on page 5 of the response that AGRAFIOTIS does teach use of several parameters (or criteria) to generate a library of compounds. Applicant argues that AGRAFIOTIS' compounds are "real" as opposed to in silico compounds. AS AGRAFIOTIS teaches that his method is computerized, and specifically teaches that his synthesis protocol generator identifies, under computer control, reagents to produce compounds with desired properties, and teaches computerized generation of a library (col. 16, lines 4-64), the examiner maintains that AGRAFIOTIS teaches/makes obvious generation of an in silico library. The criteria used by AGRAFIOTIS to generate his library include electronic and chemical bonding parameters, as well as receptor fit information. Any parameters relating to energy of a compound and/or reaction energy are "thermodynamic properties", thus AGRAFIOTIS' electronic criteria and his chemical bonding information are reasonably interpreted to be thermodynamic properties. For these reasons, the arguments are not persuasive and the rejections under 35 USC 103 are maintained.

In response to the argument that the specification does provide support for a step of generating in silico compounds using thermodynamic properties, in particular that the specification provides numerous criteria for generating compounds, and "quite clearly" teaches in silico generation of compounds, it is noted that the ONLY compounds specifically disclosed as being "synthesized" by the instant disclosure are oligonucleotides. While the specification does disclose the term "compounds", the specification does not disclose generation or synthesis, in silico or otherwise, of any other particular compounds, thus the examiner's assessment of the claims was performed "in light" of the teachings of the specification. As previously set forth, the originally filed disclosure does NOT disclose generating in silico compounds (oligonucleotide or other) based on a combination of thermodynamic and other "other" criteria anywhere. On page 3 of the response, applicant argues that it is true that one may generate sequences prior to calculating thermodynamic properties, but that "(t)his does not mean, however, that in silico compounds cannot be generated according to a thermodynamic property." The mere fact that something is possible is not the same as a specific disclosure for performing steps in the particular order now claimed. The specification does not actually teach calculation of thermodynamic properties before in silico or virtual synthesis/generation of compounds. Figure 4 indicates that virtual oligonucleotide sequences are "generated", which the examiner interprets to be an "in silico synthesis" in step 305. Step 306, which FOLLOWS step 305, is one of calculating thermodynamic, sequence and homology scores. Step 348 (which occurs after steps 305 and 306) is one of generating a LIST of those sequences with scores in a desired range. Generation of a LIST is not interpreted by the examiner to be generation or synthesis of in silico compounds/sequences; it is merely a selection of those oligonucleotides previously generated in step 305. Pages 15-18 of the specification confirm the examiner's interpretation. Pages 16-17 specifically disclose a section titled "In Silico Evaluation of Thermodynamic Properties of Virtual Oligonucleotides". Thus, while the specification and figures do provide support for in silico generation of compounds, specifically oligonucleotides, they do NOT provide support for such generation to occur "according to" thermodynamic properties. Rather, the originally filed disclosure clearly and specifically teaches calculation of thermodynamic properties AFTER in silico synthesis. For these reason, the arguments are not persuasive, and the new matter rejection is maintained.